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COMMENTARY

Catalase deficiency may complicate urate oxidase (rasburicase) therapy

LÁSZLÓ GÓTH[1] & N. WILLIAM BIGLER[2]

[1]*Department of Clinical Biochemistry Molecular Pathology and Clinical Analytical Chemistry, Medical College, Medical and Health Science Center, University of Debrecen, Debrecen PO Box 70, Hungary, H-4012, and* [2]*Center for Biomedical Laboratory Science, San Francisco State University, San Francisco, 1600 Holloway Avenue, San Francisco, CA 94132, USA*

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Abstract
Patients with low (inherited and acquired) catalase activities who are treated with infusion of uric acid oxidase because they are at risk of tumour lysis syndrome may experience very high concentrations of hydrogen peroxide. They may suffer from methemoglobinaemia and haemolytic anaemia which may be attributed either to deficiency of glucose-6-phosphate dehydrogenase or to other unknown circumstances. Data have not been reported from catalase deficient patients who were treated with uric acid oxidase. It may be hypothesized that their decreased blood catalase could lead to the increased concentration of hydrogen peroxide which may cause haemolysis and formation of methemoglobin. Blood catalase activity should be measured for patients at risk of tumour lysis syndrome prior to uric acid oxidase treatment.

Keywords: *Tumour lysis syndrome, urate acid oxidase treatment, catalase deficiency, haemolysis, blood catalase*

Primary objectives

Some patients with rapidly growing malignant neoplasms suffer from life threatening tumour lysis syndrome [1]. Tumour lysis syndrome can occur prior to anti-neoplastic therapy but is more commonly linked to cell lysis following chemotherapy or radiation therapy. This syndrome is thought to be due to high circulating concentrations of intracellular products that are released by cell lysis and severe hyperuricaemia, hyperkalaemia and hyperphosphataemia occur. Obstructive uropathy and renal failure in tumour lysis syndrome patients may be due to the low solubility of uric acid and high concentrations of urate [2].

Tumour lysis syndrome patients with hyperuricaemia are treated with allopurinol, which inhibits urate synthesis but does not enhance elimination of existing urate. Recently, the urate oxidase therapy seems to substitute allopurinol therapy.

In this note we suggest that a successful prophylactic therapy with urate oxidase, against tumour lysis syndrome may be contraindicated for patients with deficiency of the enzyme catalase and that blood catalase activity should be measured before the therapy is initiated.

Outcomes and results

Infusion of uric acid/urate oxidase has been more successful than previous therapies for lowering urate concentrations in tumour lysis syndrome patients [2,3]. Rasburicase is the first recombinant urolytic enzyme which is a useful option for prophylaxis and treatment of anti-cancer therapy induced hyperuricaemia in adult, paediatric and neonates patients

Correspondence: L Góth, Department of Clinical Biochemistry Molecular Pathology and Clinical Analytical Chemistry, Medical and Health Science Center, University of Debrecen, Debrecen PO Box 70, Hungary, H-4012. Tel: +36-52-340-006/55995. Fax: +36-52-417-631. E-mail: goth@dote.hu

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[4–8]. It may be a challenge for rheumatologists in severe tophaceous gout [9]. Uric acid oxidase catalyses the oxidation of urate to allantoin and hydrogen peroxide. Allantoin, which is much more soluble than uric acid, is readily released through the kidneys. Catalase is the primary means for decomposition of hydrogen peroxide to water and oxygen [10,11].

In clinical trials, rasburicase caused (< 1%) haemolytic anaemia, methemoglobinaemia and increased serum LDH activity. These side effects are secondary to the oxidative stress created by hydrogen peroxide produced during this therapy [2,12–16]. A few patients with methemoglobinaemia had a genetic deficiency of glucose-6-phosphate dehydrogenase and the FDA recommended to screen patients for deficiency of glucose-6-phosphate dehydrogenase prior to this therapy. The other patients with normal glucose-6-phosphate dehydrogenase activities had no explanation for methemoglobinaemia or for haemolysis.

In normal individuals extracellular hydrogen peroxide readily diffuses into erythrocytes, where it is decomposed by catalase [17]. In cases of glucose-6-phosphate dehydrogenase deficiency and catalase deficiency, oxidative stress can cause severe damage to erythrocytes [18,19].

The plasma hydrogen peroxide concentration is up to 35 μmol/L [20]. Uric acid oxidase therapy may cause a hydrogen peroxide shock when its concentration increases to ~500 μmol/L or higher. In case of catalase deficiency (acquired or inherited) this high concentration of hydrogen peroxide can cause haemolysis.

Frequent decrease of catalase occurs in serious anaemia, when blood haemoglobin concentration is ~70 g/L the blood catalase activity is less than 58% [21].

The first detection of the inherited catalase deficiency (acatalasaemia) happened in Asia (Japan: 1948, Korea: 1968, Iran: 1984) then in America (USA: 1963, Mexico: 1974, Peru: 1977, Canada: 1995) and in Europe (Switzerland: 1961, Israel: 1963, Germany: 1977, Austria: 1988, Hungary: 1992). Frequency of acatalasaemia (homozygous state) is 0.04–0.8/1000 and that of hypocatalasaemia (heterozygous state) is 2–4/1000. To date ~114 cases of acatalasaemia have been reported in 61 families from 12 countries. The patients with acatalasaemia in Japan (90), Switzerland (11) and Hungary (2) have been characterized while the other cases have been sporadic and relatively poorly characterized [22].

In Hungary, individuals with inherited heterozygous ($n = 61$) and homozygous ($n = 2$) deficiency of catalase have average activities of 52% and 5% of the median reference range value for blood catalase, respectively. The frequencies of homozygous and frequencies heterozygous patients are 2–3 per 1000 and 0.04–0.08 per 1000, respectively [22]. These patients showed the higher prevalence of diabetes mellitus [23] and abnormal lipid concentrations [24] without chronic haemolysis [25].

We found no papers in the literature on the direct toxic effect of hydrogen peroxide shock generated during the urate oxidase therapy in catalase deficient patients. There is only a recently released paper which demonstrates highly increased methemoglobin concentration due to external hydrogen peroxide for a Japanese acatalasaemic patient [26]. Furthermore, in two cases of rasburicase induced methemoglobinaemia the catalase deficiency was supposed for a possible explanation but it was not measured [27].

Conclusions

The tumour lysis syndrome patients with unexplained haemolytic anaemia following uric acid oxidase infusion could have been catalase deficient patients.

Blood catalase activity determination indicates its usefulness for selecting these patients to prevent situations associated with toxic concentrations of hydrogen peroxide [28]. Therefore, catalase deficiency may be suggested as a further criterion before initiation of uric acid oxidase therapy.

Acquired catalase deficiency due to severe anaemia may be compensated with blood transfusion prior to chemotherapy.

Currently, screening chemotherapy patients for inherited catalase deficiency is not feasible because catalase assays are not performed in clinical laboratories.

Oncology services could implement a simple qualitative test to detect homozygous deficiencies [26,29]. Positive results would alert clinicians to monitor carefully for signs of haemolysis and methemoglobinaemia. They can use either a lower rate of infusion or other therapy than uric acid oxidase to avoid its complications due to hydrogen peroxide shock.

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